The Parkin-like ubiquitin E3 ligase Ariadne-1 in the mammalian brain: Potential implications for neurodegenerative disease

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Abstract

Parkinson's disease (PD) is a movement disorder characterized by a massive loss of dopaminergic neurons of nigrostriatal origins. Several genes associated with familial cases of PD encode proteins that are direct components of the 26S Ubiquitin Proteasome System (UPS) or interact with enzymes involved in the UPS. Of these genes, *parkin*, and its product Parkin, an ubiquitin E3 ligase, is the most well characterized. Loss-of-function mutations in *parkin* result in the "early onset" PD known as Autosomal Recessive Juvenile Parkinsonism (AR-JP). Most research has focused on studying in what ways do nigrostriatal dopaminergic neurons differ from other neurons in the brain and how and why do these cells die in PD. In the following report I describe studies addressing the equally important alternative question: How do other neurons of the brain differ from nigrostriatal dopaminergic neurons that allow them to survive in AR-JP? I hypothesize that another E3 ligase provides redundant functions to Parkin in surviving neurons but that this redundant UPS enzyme is absent from dopaminergic neurons of the SNC. One protein that could possibly provide such a redundant function is the Parkin-like E3 ligase, Ariadne-1. Ariadne-1 and Parkin share significant sequence identity and similarity; they share the RING-IBR-RING signature domain; they share some UPS E2 enzymes; and they bind some of the substrates. ^ In this dissertation I show Ariadne-1 to be a component of LB in post-mortem human tissue of various neurodegenerative disease. Then, in rats, I determine that Ariadne-1 is present as both mRNA and protein in cells of the SNC. Furthermore, Ariadne-1 is globally expressed throughout the mammalian brain and this expression is restricted to neurons and absent from glial cells and white matter tracts. I also find that only a subset of nigrostriatal dopaminergic neurons express Ariadne-1. Then, using the PD model of unilateral striatal lesioning of mice, I determine that Ariadne-1 expression actually correlates more closely with an increased susceptibility to oxidative stress-induced cell death. Lastly, using two different *parkin*$^{-/-}$ mice, I determine that, in the absence of Parkin, Ariadne-1 expression correlates with a measurable advantage to dopaminergic neurons of the SNC.^

Subject Area

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